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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,500	11/03/2000	Herve Recipon	DEX-0087	6616

7590 06/19/2003
Kathleen A Tyrrell
Liicata & Tryrell P C
66 E Main Street
Marlton, NJ 08053

EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 06/19/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/705,500

Applicant(s)
Recipon et al

Examiner
Karen Canella

Art Unit
1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 months MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 12 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18 6) ☒ Other: Attachment

Art Unit: 1642

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 24, 2003 has been entered.
2. Claims 1-5 and 12 are pending.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Grounds of Rejection

4. Claims 2 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "identifying a patient having cancer that is not known to have metastasized" and "determining the Lng108 level in the cells, tissues or bodily fluid from said patient" and "wherein an increase in the Lng108 level in the patient versus the normal human control is associated with cancer which has metastasized". It is unclear what applicant is trying to claim, as the method requires a patient free of metastases in section (a) yet an association with the presence of metastatic cancer is made in section (c). For purpose of examination, section (a) will not be considered as limiting.

5. Claims 1 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing the presence of cancer or metastases in patients by measuring an increase in the level of the Lng108, does not reasonably provide enablement for methods of diagnosing the presence of cancer or metastases in patients by

Art Unit: 1642

measuring an change in the level of the Lng108 which is not an increase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claim 1 is drawn to a method of diagnosing the presence of cancer in a patient comprising comparing the level of Lng108 in cells, tissues or bodily fluids of a patient with levels of Lng108 in the corresponding tissues and fluids of a normal human control, wherein a change in determined in Lng108 in the cells, tissues or bodily fluids of the patient is indicative of cancer, especially metastatic cancer. The specification and subsequent declaration have stated that the Lng108 polypeptide is a marker for cancer cells, particularly metastatic cancer cells and thus is present at an elevated level within cancer cells, metastatic cancers cells and bodily fluids of the patients having said cancer cells. When given the broadest reasonable interpretation, "a change" reads on a decrease as well as an increase. Thus claim 1 is drawn to a method of diagnosis wherein the Lng108 expression level is decreased in cancerous or metastatic cells. There are no teachings in the specification to support the notion that loss of expression of the Lng108 protein would be indicative of a cancerous or metastatic state. Thus, one of skill in the art would be subject to undue experimentation in order to use the broadly claimed method.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent,; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Art Unit: 1642

7. Claims 1, 2 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Olsen et al (Pub No. US 2002/0042372 A, priority to October 27, 1999) as evidenced by the enclosed alignment of the instant amino acid sequence of SEQ ID NO:3 and polynucleotide of Sequence 1.

Claim 1 is drawn to a method for diagnosing the presence of cancer in a patient comprising determining the level of Lng108 in cells, tissues or bodily fluids in a patient; and comprising the determined levels of Lng108 with levels of Lng108 in cells, tissues or bodily fluids from a normal human control, wherein a change in determined levels of Lng108 in said patient versus normal human control is associated with the presence of cancer and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. Claim 2 is drawn to a method of diagnosing metastases of cancer in a patient comprising determining Lng108 levels in a sample of cells, tissues or bodily fluids from a patient; and comprising said Lng108 levels with the Lng108 levels in the cells, tissues or bodily fluids of a normal human control, wherein an increase in the Lng108 levels in said patient is associated with a cancer which has metastasized, and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. Claim 12 is drawn in part to the methods of claims 1 and 2 wherein the cancer is lung cancer.

Olsen et al disclose methods of detecting cancer and metastatic cancer comprising detecting stanniocalcin [0382, 0400, 0402, 0421, 0423, 0427, 0428]. Olsen et al specifically disclose the detection of metastases of lung carcinoma ([0428] "Additionally diseases or conditions associated with increased cell survival that could be ...detected by stanniocalcin polynucleotides or polypeptides...include but are not limited to progression and/or metastasis of malignancies ...such as leukemia and solid tumors including...lung carcinoma [and] small cell lung carcinoma...").

Art Unit: 1642

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen et al (Pub No. US 2002/0042372 A) in view of Sobol et al (U.S. 5,543,296) as evidenced by the enclosed alignment of the instant amino acid sequence of SEQ ID NO:3 and polynucleotide of Sequence 1.

Claim 3 is drawn to a method of staging cancer in a patient having cancer comprising: determining Lng108 levels in a sample of cells, tissues or bodily fluids from a patient; and comprising said Lng108 levels with the Lng108 levels in the cells, tissues or bodily fluids of a normal human control, wherein an increase in the Lng108 levels in said patient is associated with a cancer which is progressing and a decrease in the Lng108 levels is associated with a cancer which is regressing or in remission, and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence

Art Unit: 1642

of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

Claim 4 is drawn to a method of monitoring cancer in a patient for the onset of metastasis comprising identifying a patient having cancer that is not known to have metastasized; periodically determining levels of Lng108 levels in samples of cells, tissues or bodily fluids from said patient; and comparing the periodically determined levels of Lng108 with the levels of Lng108 for the cells, tissues or bodily fluid or a normal human control; wherein an increase in any one of the periodically determined Lng108 levels in the patient versus the control is associated with a cancer which has metastasized and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. Claim 5 is drawn to a method of monitoring a change in stage of cancer in a patient comprising: identifying a patient having cancer that is not known to have metastasized; periodically determining levels of Lng108 levels in samples of cells, tissues or bodily fluids from said patient; and comparing the periodically determined levels of Lng108 with the levels of Lng108 for the cells, tissues or bodily fluid or a normal human control; wherein an increase in any one of the periodically determined Lng108 levels in the patient versus the control is associated with a cancer which is progressing in stage and a decrease is associated with a cancer which is regressing in stage or in remission, and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. Claim 12 embodies the methods of claims 1, 2, 3, 4 and 5 wherein the cancer is lung cancer. The specific embodiments of claims 1 and 2 are set forth above.

The enclosed alignment indicates that the instant amino acid sequence of Lng108, SEQ ID NO:3, is encoded by Sequence 1 of Olsen et al. Olsen et al terms the amino acid encoded by Sequence 1 as stanniocalcin.

Art Unit: 1642

Olsen et al teach a method for detecting lung cancer and metastatic lung cancers and other cancers and metastatic cancers comprising the detection of the Lng108 polypeptides and/or polynucleotides, for the reasons set forth above. Olsen et al do not specifically teach method steps which recite the staging of cancer or method steps which are repeated over time to determine the progression of cancer.

Sobol et al teach that recent advances in cancer therapeutics have demonstrated the need for more sensitive staging and monitoring procedures to ensure initiation of appropriate treatment, to define the end points of therapy and to develop and evaluate novel treatment modalities and strategies, but that conventional methods to detect distant metastases do not have adequate sensitivity (column 1, lines 27-41). Sobol et al teach that because of this lack of sensitive method for detecting metastases, 25% to 30% of patients having non-small cell lung cancer who are classified as having Stage I disease actually have metastatic lesions that are not detected and that these individuals are not cured by primary tumor resection (column 1, lines 42-67). Sobol et al teach the necessity of adequate staging methods for the management of both non-small cell lung cancer and small cell lung cancer (column 2, lines 1-18). Sobol et al teach that small cell lung cancer patients generally have metastatic disease at the time of diagnosis. Sobol et al teach that current staging procedures cannot distinguish SCLC patients who will have earlier relapses despite achieving initial complete remission, because most patients who have initial complete remission have minimal residual disease which cannot be detected by conventional methods and that more sensitive methods are needed to detect metastases and thereby identify patients at high risk for early tumor recurrence who may benefit from additional systemic therapy.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to monitor patients having cancer, and especially lung cancer over time for the presence of Lng108 in cells, tissues and bodily fluids in order to stage the progress of the cancer. . One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Sobol et al on the necessity of monitoring for the

Art Unit: 1642

presence of metastases in patients having lung cancer in order to provide such patients who develop metastatic lesions with appropriate systemic therapy, beyond that of primary surgical resection.

10. The rejection of claims 1-5 and 12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. Claims 1-5 and 12 are drawn in part to methods for diagnosing the presence of cancer based on the detection of Lng108, wherein Lng108 comprises a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or SEQ ID NO:2. The recitation of "stringent conditions" without the definition of what constitutes the physical conditions of stringent hybridization does not serve to limit the structure of the hybridizing polynucleotides. The specification does not set forth any written description of these hybridizing polynucleotides which could vary in length and sequence.

The disclosure of a single species may provide an adequate written description of a genus when the species disclosed is representative of the genus. The instant claims encompass allelic sequences, splice variants, and homologs which are not fully described. There is substantial variability among the species nucleic acids encompassed within the scope of the claims because they are not limited by a common structural feature or a defined function. Thus SEQ ID NO:1 or 2 are not descriptive of variant nucleic acids of SEQ ID NO:1 or 2 or fragments of SEQ ID NO:1 or 2.. Thus the claimed method relies on the detection on a large genus of polynucleotides.

A description of a genus of nucleic acids may be achieved by means of recitation of a representative number of nucleic acids, defined by nucleic acid sequences, falling within the scope of the genus or a recitation of structural features common to members of the genus, which

Art Unit: 1642

features constitute a substantial portion of the genus. (Reagents of the University of California v. Eli Lilly, 119 F3d 1559, 1569, 43 USPQ2d 1398-1406, Fed. Cir. 1997).

The written description sets forth only SEQ ID NO:1 or 2. Therefore there is no disclosure of a single common structural feature shared by members of the claimed genus. Since the claimed genus encompasses genes yet to be discovered and the polynucleotide encoding SEQ ID NO:1 and 2 do not "constitute a substantial portion" of the claimed genus. Thus, for the reasons set forth above, the specification fails to provide an adequate written description for the methods which rely on polynucleotides which hybridize to an antisense sequence of SEQ ID NO:1 or 2.

Applicant argues that the polynucleotides determined in the claimed methods of the present invention either comprise SEQ ID NO:1 or 2, hybridize under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or express the same protein as thus said polynucleotides are in possession of structural and functional limitations supportive of the genus claimed. Applicant further argues that in the molecular biology arts it is unnecessary to provide explicit disclosure of all the nucleic acid sequences that encode amino acid sequences. This has been considered but not found persuasive. The limitations of the claims encompass the hybridization under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2. Neither the specification nor the claims limits this stringent hybridization to "highly stringent" nor is there a limitation with respect to the length or the apparent molecular weight of the encoded species. When given the broadest reasonable interpretation the stringent hybridization encompasses low, medium and high stringency hybridization and thus reads on proteins and nucleic acids which differ significantly in amino acid sequence from the instant SEQ ID NO:3. With regard to degenerate coding sequences, hybridization conditions are not limiting to nucleic acid sequences which differ only in codon usage from the instant SEQ ID NO:1 or 2 as mismatches may occur at any position of the reading frame and are not restricted to every third nucleotide. If applicant only intends to use this claim language to claim degenerate coding sequences, it is recommended that

Art Unit: 1642

the claim be amended to substitute, --polynucleotides which encode SEQ ID NO:3--- for polynucleotides which hybridize under stringent conditions to an antisense nucleic acid of SEQ ID NO:1 or 2.

11. All other rejections and objections as stated in Paper no. 15 are withdrawn.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 14, 2003

[illegible]

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Db 616 CACTGTGCGCAAAACACCCACGAGCTGACTTCAACGAGACGCAACCAATGAACCTCAG 875
 QY 221 LysLeuLysValLeuLeuArgAsnLeuArgGlyGluLysAspSerProSerHisIleLys 240
 Db 676 AAGCTGAAGTCTCTCTCTCAGGAACCTCGAGGTGAGGAGACTCTCTCTCCACATCAA 735
 QY 241 ArgThrSerHisGluSerAla 247
 Db 736 CGCACATCCCATGAGAGTCA 756
 RESULT 2
 US-09-840-989A-1
 ; Sequence 1, Application US/09840989A
 ; Patent No. US20020042372A1
 ; GENERAL INFORMATION:
 ; APPLICANT: Olsen et al.
 ; TITLE OF INVENTION: stannicalcin Polynucleotides, polypeptides, and Methods Based Th
 ; FILE REFERENCE: PFI08P2
 ; CURRENT APPLICATION NUMBER: US/09/840.989A

181 SerLeuMetGluLysILEGlyProAsnMetAlaSerLeuPheHisILEuGlnThrAsp 200

474 AACGGGTCACCTCCAAAGTCTTCTCGCCATTGGAGGTGCTCCACTTTCCAAAGATG 533

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